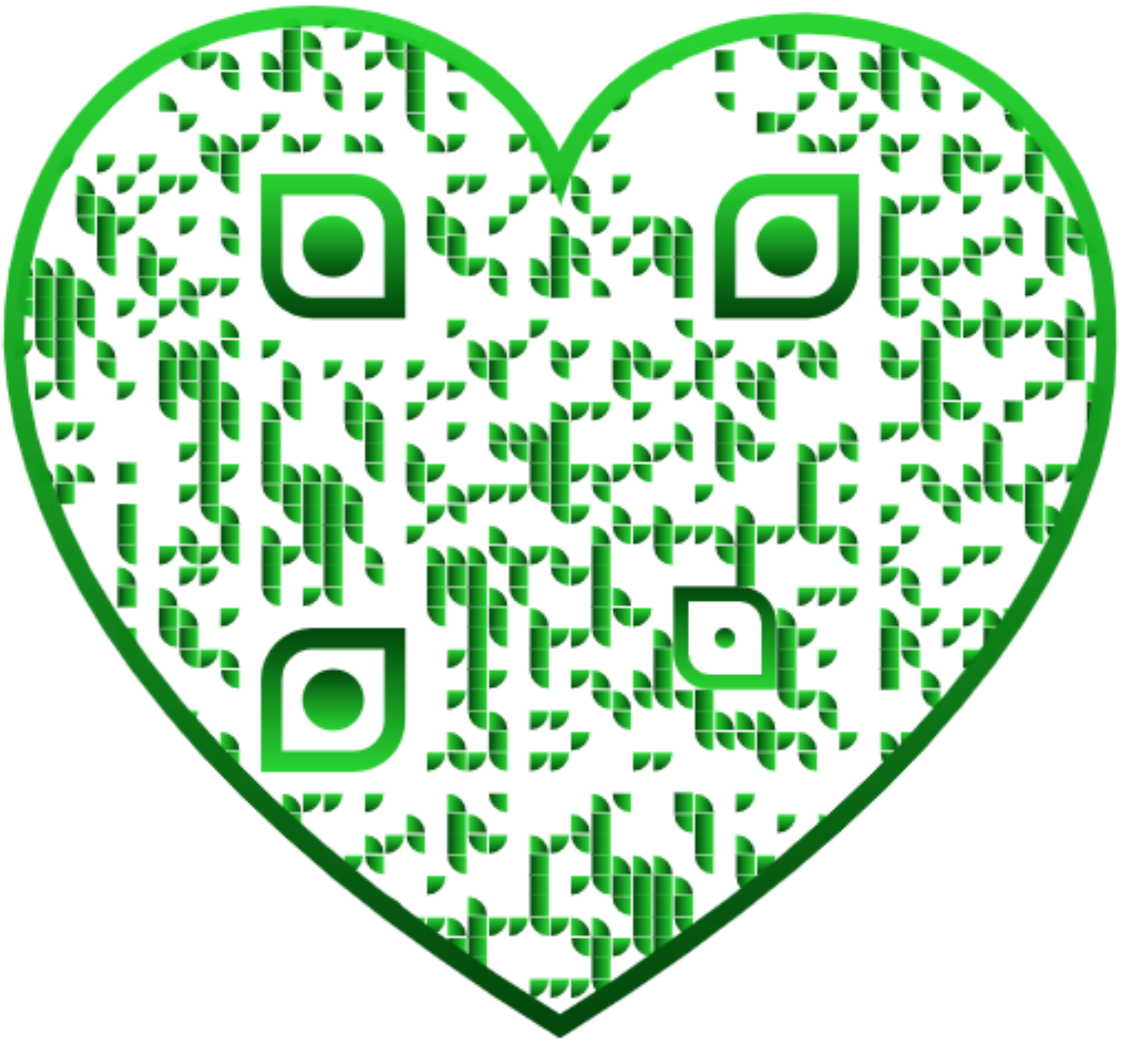
2.8 Dosage Regimen



Introduction

- Dosage regimen
  - This is a formalized schedule by which drugs are administered,
  - It includes the dosage form, dosing rate, dose, dose interval between doses, route of administration, and duration of therapy
- The success of drug therapy is highly dependent on the choice of the drug and drug product and on the design of the dosage regimen.

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- Therapeutics must be dominated by objective evaluation of an adequate base of factual knowledge.
  - This philosophy has been popularized recently under the terminology of "**evidence-based medicine**".
- In clinical practice, pharmacokinetic principles are used to characterize the relationships between drug dosage regimens and drug concentration–time profiles.

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- When starting a patient on a particular drug therapy, the clinician is dependent on general dosing information.
    - Here, the clinician cannot know exactly how this specific patient will react to the drug, Pharmacokinetically or Pharmacodynamically.
- Optimal therapeutic outcome is a term that has been used to describe "the right drug, to the right patient, at the right time"

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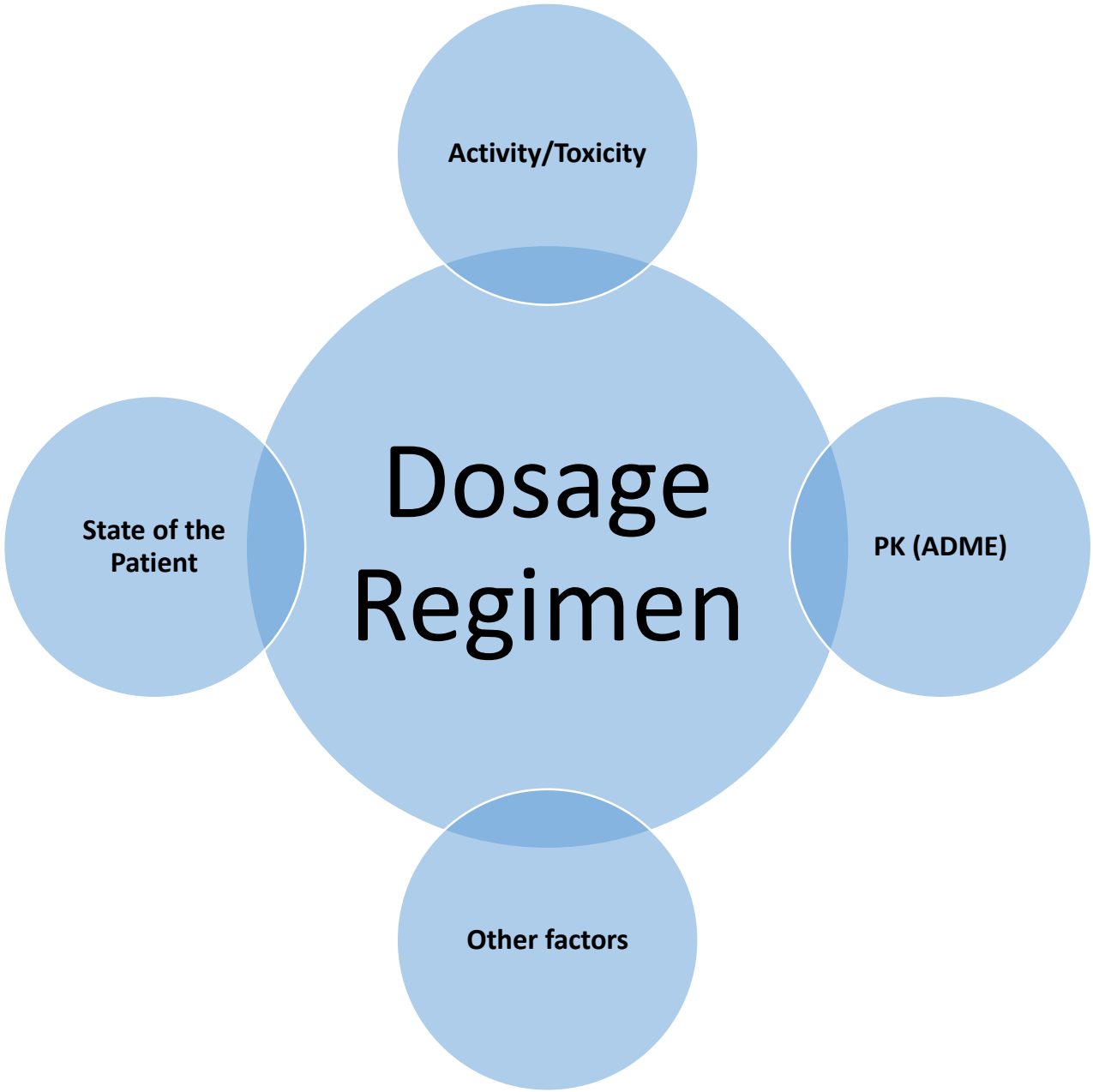
- Different factors affect drug response (drug selection).
    - Pharmacodynamic factors
    - Pharmacokinetic factors (Factors affecting ADME processes)
    - Patient related factors
- Dosage regimens are generally derived using average pharmacokinetic parameters to maintain plasma concentrations of the drug within the therapeutic window.
    - The above factors must be taken into consideration for maintaining desired therapeutic concentrations of a drug


Activity/Toxicity
State of the Patient
Dosage Regimen
PK (ADME)
Other factors

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- Dosage regimens are designed to produce a therapeutic objective.
    - This objective may be achieved by various modalities of drug administration, extending from a single occasional dose to continuous and constant input.
- In other words, treatment of patients with varies disease or conditions with drugs often requires the maintenance of systemic exposure.

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- Treatment of patients with varies disease or conditions with drugs often requires the maintenance of systemic exposure,
- To do so, drug may be given by:
    - Constant-rate protocol (Constant-rate Regimen)
    - Repeated administration (Multiple-dosage Regimen)
- A therapeutic concentration is appropriately defined in terms of an individual patient's requirement.
    - Usually, this information is unknown on initiating therapy.

Constant-rate Regimen

- A single dose may rapidly produce a desired therapeutic concentration,
  - But this mode of administration is unsuitable when maintenance of plasma or tissue concentrations and effect is desired.
- To maintain a constant plasma concentration, drug must be administered at constant rate.
- Could be done with
  - Constant rate intravenous infusion or
  - Constant rate release devices (extra-vascular)

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- A wider application of constant-rate therapy become possible with the development and use of constant-rate release devices.

- Revise the calculation for the different PK parameters during:

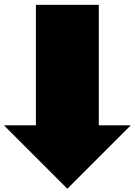
  - Constant rate infusion

  - IV bolus + Constant rate infusion

Multiple-dosage Regimen

- Although constant-rate regimens possess many desirable features, they are not the most common ones.

- The more common approach to the maintenance of continuous therapy is to give multiple discrete doses.



Multiple dosage regimen

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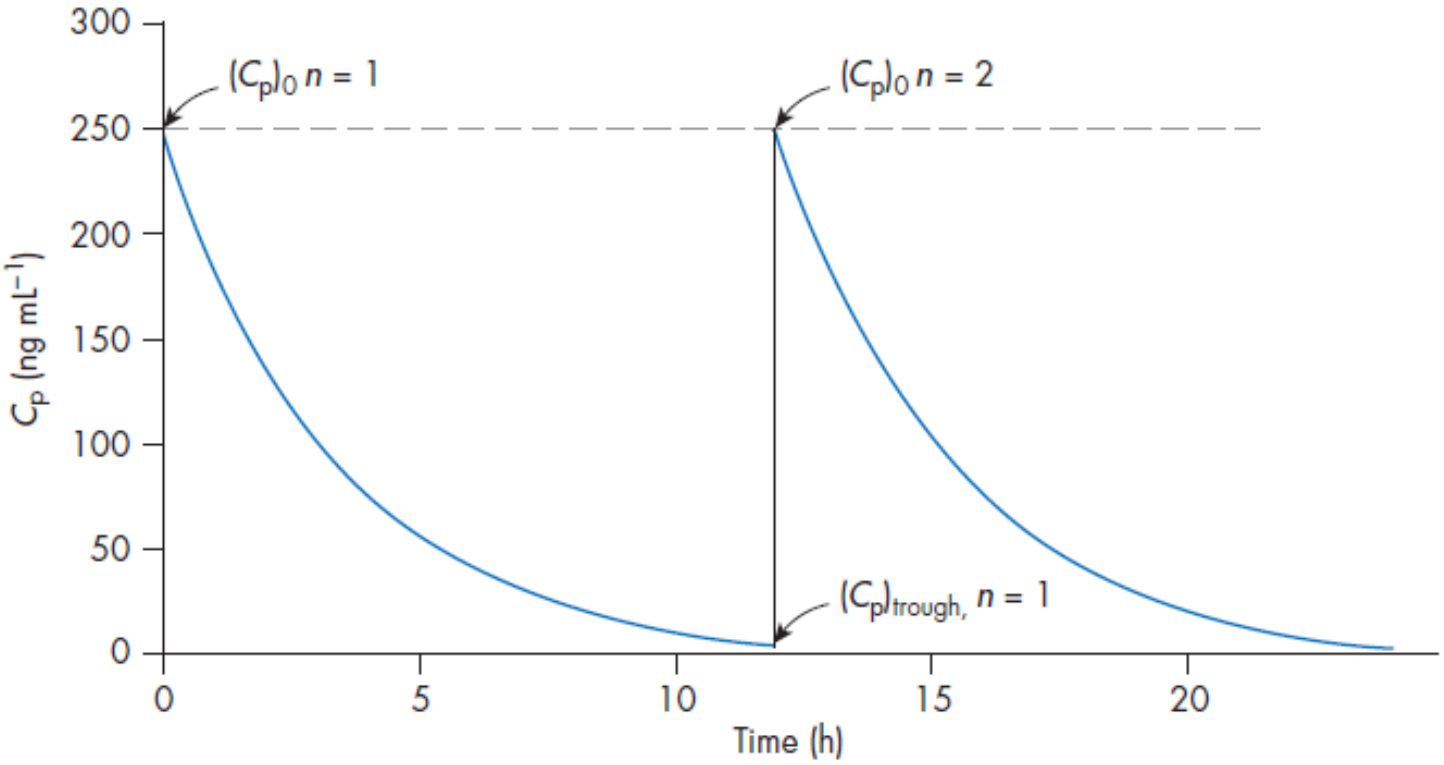
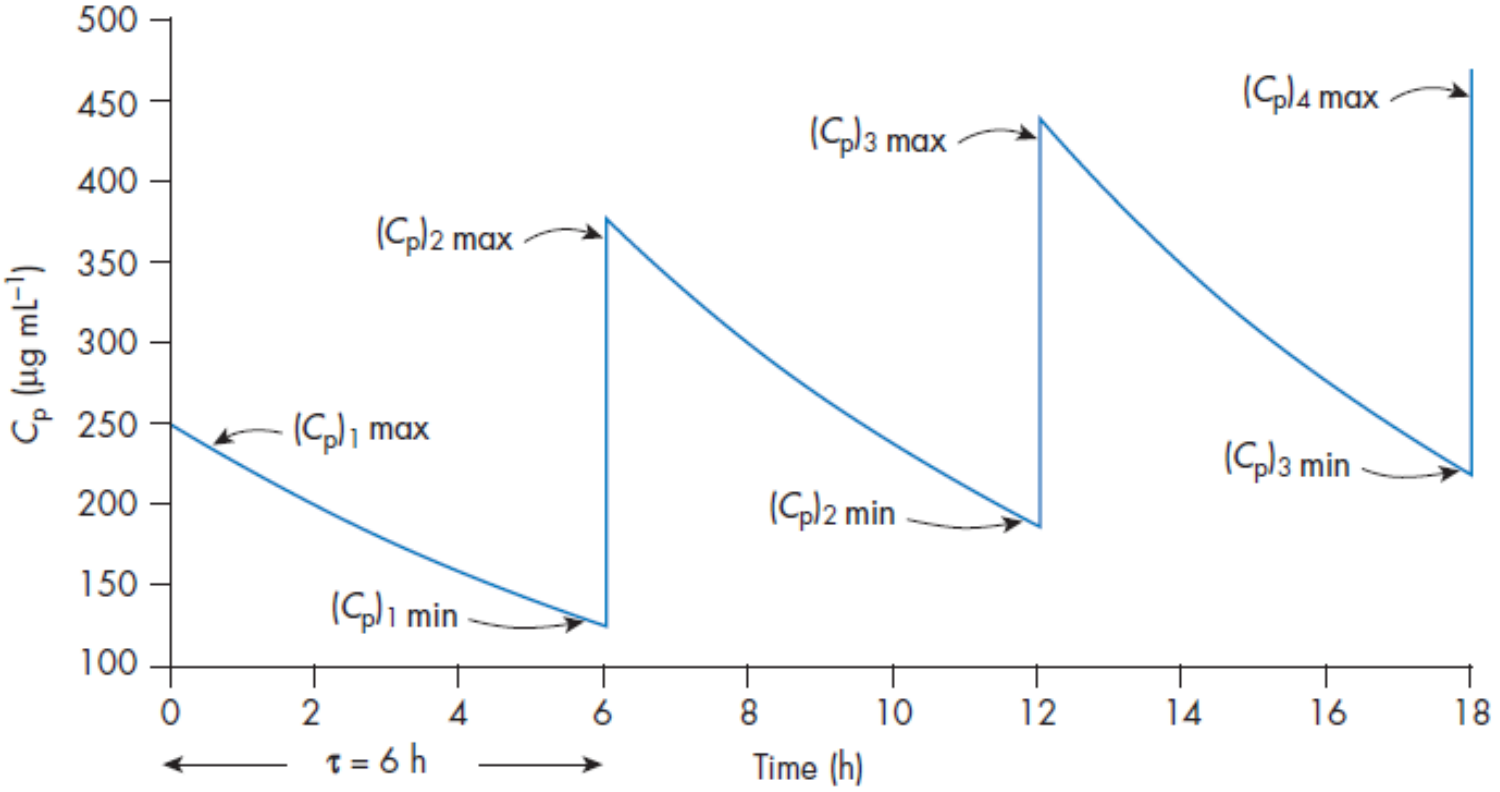
Multiple dosing concepts

- Peak plasma level, following the administration of each succeeding dose, is higher than the peak concentration following the administration of the first dose.
- This phenomenon is the consequence of drug **accumulation** in the body relative to the first dose.
- Following the administration of a number of doses, a steady state condition will be achieved.



Next dose is administered when there is essentially no drug accumulation in the body; in other words, there is no drug left in the body from previous doses.



Next doses are administered at finite time intervals.

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- In obtaining the different parameters for multiple dosing, the following theoretical **assumptions** are made:
  - Linear pharmacokinetics applies; that is, the rate process obeys passive diffusion and first order elimination kinetics.
  - Tissues can take up an infinite amount of drug, if necessary.
  - The apparent volume of distribution (V), elimination half life ($t_{1/2}$) and the elimination rate constant (K) are independent of the number of administered doses.

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- The time interval between dosing or successive doses is constant.
- The administered dose is equal at each successive time interval.

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- Useful pharmacokinetic parameters in multiple dosing include:
  - The Dost ratio (r)
  - The concentration of drug in the body at any time t during the dosing interval.
  - The steady-state plasma concentrations.
  - The maximum and minimum plasma concentrations at steady state.

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- The "average" steady-state plasma concentration,
- Drug accumulation (R),
- Fluctuation (Φ),
- Number of doses (n) required to attain a given fraction of steady state (f_{ss})
- Loading (D_L) and maintenance dose (D_M)

Multiple-dosage Regimen: IV Administration

A single IV bolus dose

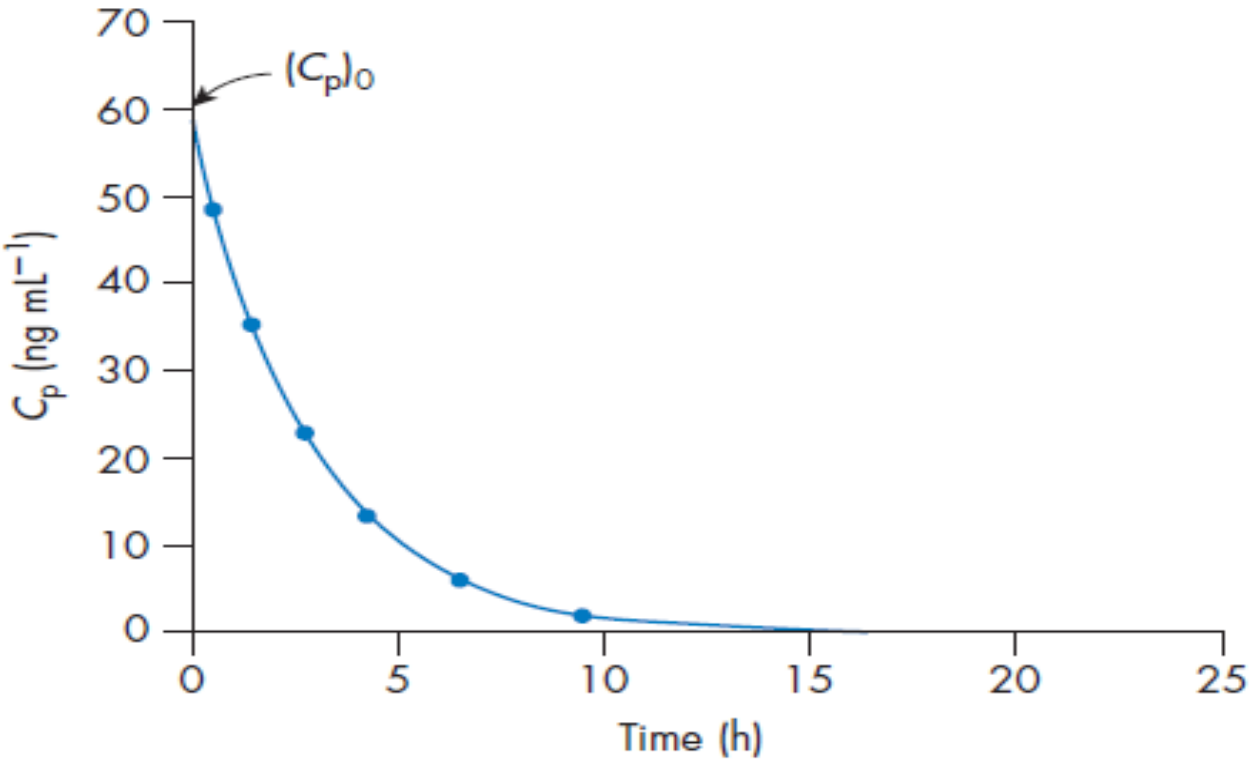
- Over time after an IV bolus dose, the amount and concentration of the drug in the body is given by:

$$X = X_O e^{-Kt}$$

And,

$$C_p = \left(C_p\right)_O e^{-Kt}$$

- From such administration;
  - At t = 0,
    - $X = X_O$
    - $C_p = (C_p)_O$ (i.e. maximum or peak plasma concentration, or intercept of the concentration versus time plot) and,
  - At $t = \infty$
    - $X = 0$ and $C_p = 0$.



A typical plasma concentration versus time profile for a single IV bolus dose of a drug that follows first-order elimination and has one compartment distribution.

Multiple IV bolus dose

The Dost ratio (r)

- The Dost ratio permits the determination of the X and/or the C_p of a drug in the body at any time t following the administration of the n^{th} dose.

- In other words, this ratio will transform a single dose equation into a multiple-dosing equation.

$$r = \frac{1 - e^{-nK\tau}}{1 - e^{-K\tau}}$$

Where, n is number of administered doses; K is the first-order elimination rate constant; and τ is the dosing interval

Plasma concentration at any time t: $\left(C_{pn}\right)_t$

- To determine the plasma concentration of a drug in the body at any time, t, following administration of the nth dose:
  - Inserting the Dost ratio between $\left(C_p\right)_o and\ e^{-Kt}$ in the equation $C_p = \left(C_p\right)_o e^{-Kt}$

$$\left(C_{pn}\right)_t = \left(C_p\right)_o \frac{\left(1 - e^{-nK\tau}\right)}{\left(1 - e^{-K\tau}\right)} e^{-Kt}$$

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- From the above equation,
  - When n = 1, (i.e. administration of the first dose)

$$\left(C_{pn}\right)_t = \left(C_p\right)_O \frac{(1 - e^{-nK\tau})}{(1 - e^{K\tau})} e^{-Kt} \quad \rightarrow \quad C_p = \left(C_p\right)_O e^{-Kt}$$

  - When $n = \infty$ (i.e. administration of many doses; generally more than eight or nine), $e^{nK\tau} = 0$

- **Note**: t in multiple dose PK is the time since the latest (n^{th}) dose was given (i.e. $t \geq 0 \; and \; t < \tau$) (a value between dosing interval).

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- At t = 0, $e^{-Kt} = 1$,
  - The plasma concentration at this time is the maximum plasma concentration $\left(C_p\right)_{max}$.
  - Therefore,

$$\left(C_{pn}\right)_{max} = \frac{\left(C_p\right)_O (1 - e^{-nK\tau})}{(1 - e^{-K\tau})}$$

  - This Eq. represents the maximum plasma concentration of a drug in the body following the administration of the n^{th} dose.
  - Referred as "**peak**" plasma concentration.

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- At $t = \tau$,
  - The body will display the minimum plasma concentration, $(C_p)_{min}$, of a drug.

$$(C_{pn})_{min} = \frac{(C_p)_O (1 - e^{-nK\tau})}{(1 - e^{-K\tau})} e^{-K\tau}$$

  - This Eq. represents the minimum plasma concentration of a drug in the body following administration of the n^{th} dose.
  - Referred as "**trough**" plasma concentration.

Steady-state plasma concentration

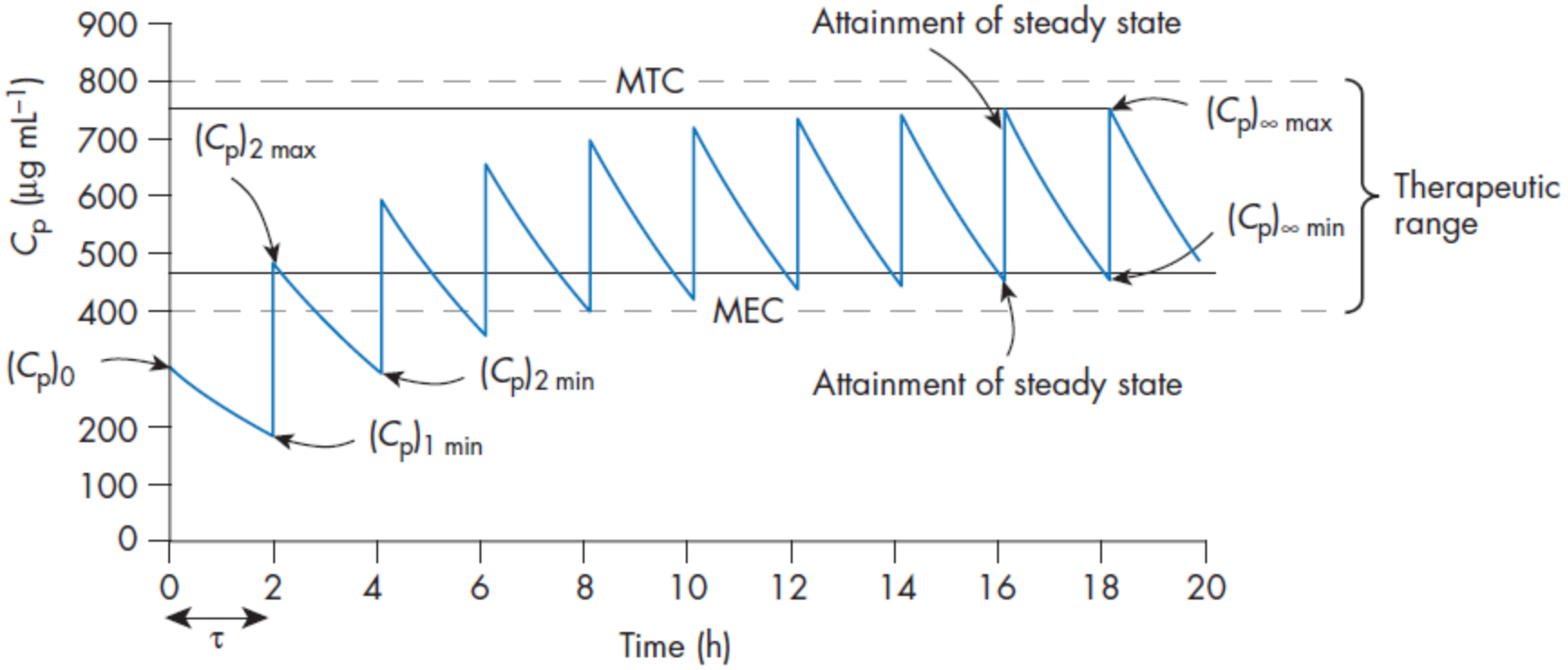
- The steady-state condition is attained following the administration of many doses (i.e. $n = \infty$).

- When $n \to \infty, e^{-nK\tau} \to 0$, then

$$\left(C_{pn}\right)_t = \frac{\left(C_p\right)_O (1 - e^{-nK\tau})}{(1 - e^{-K\tau})} e^{-Kt} \to \left(C_{p\infty}\right)_t = \frac{\left(C_p\right)_O}{(1 - e^{-K\tau})} e^{-Kt}$$

- This Eq. represents the plasma concentration of drug in the body at any time t following the attainment of steady state.

The $(C_{pn})_{max}$ and $(C_{pn})_{min}$ at steady state



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- For drugs administered IV,
  - The maximum steady-state plasma concentrations will occur only at t = 0 (immediately after administration of the latest bolus dose).

$$\left(C_{p\infty}\right)_{max} or \left(C_{pss}\right)_{max} = \frac{\left(C_p\right)_O}{\left(1 - e^{-K\tau}\right)}$$

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- And, the minimum steady-state plasma concentrations will occur only at t = τ (immediately after administration of the latest bolus dose).

$$\left(C_{p\infty}\right)_{min} or \left(C_{pss}\right)_{min} = \frac{\left(C_p\right)_O}{\left(1 - e^{K\tau}\right)} e^{-K\tau}$$

Or

$$\left(C_{pss}\right)_{min} = \left(C_{pss}\right)_{max} e^{-K\tau}$$

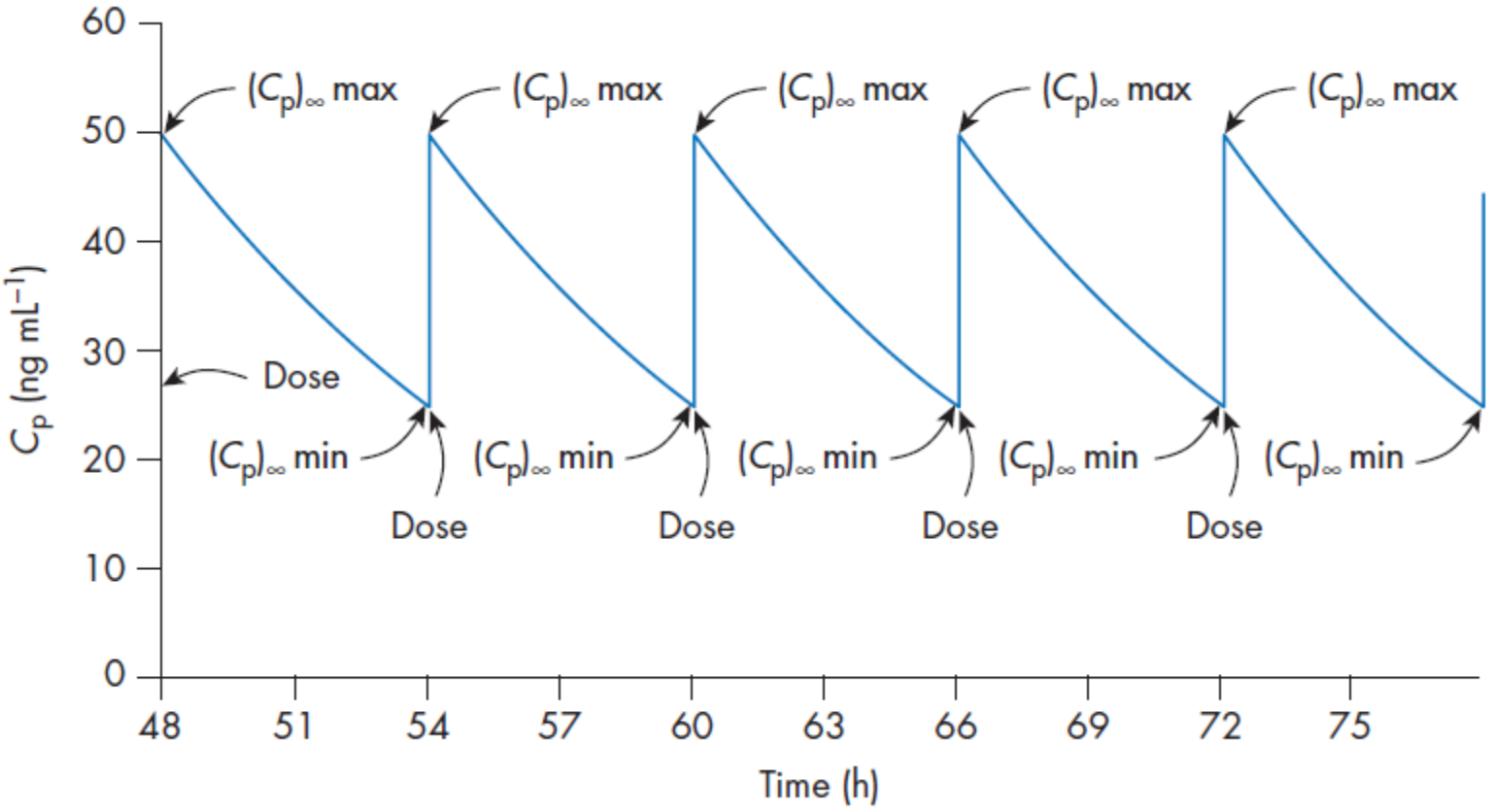

Fig. Cp vs t profile following the attainment of steady-state condition for a drug administered by multiple intravenous bolus injections.

The "Average" plasma concentration at steady state

- A very useful parameter in multiple dosing.
- This plasma concentration value will fall between the maximum and minimum steady-state plasma concentration values.
  - It is the one desired therapeutically for patients on a regular dosage regimen.

$$\left(\bar{C}_p\right)_{ss} = \frac{\int_0^{\tau} C_{p\infty}\, dt}{\tau}$$

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- The term $\int_0^{\tau} C_{p_\infty} dt$ is the AUC at steady state during dosing interval.

$$AUC = \int_0^{\tau} C_{p_\infty} dt = \frac{X_O}{VK}$$

- Therefore,

$$\left(\bar{C}_p\right)_{ss} = \frac{X_O}{VK\tau}$$

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- Designing or establishing the dosage regimen for a drug:
  - Know the therapeutic range and/or the effective concentration range for the drug;
  - Select the desired or targeted "average" steady-state plasma concentration (commonly the mean of the therapeutic range);
  - Select the dosing interval (it is a safe and good practice to start with a dosing interval equal to the drug's elimination half life).
  - Calculate the dose (X_0) needed to attain the desired "average" steady-state concentration.

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- Then, calculate the "average" steady-state concentration, peak steady-state concentration and trough steady-state concentration;

- Make sure that the calculated peak steady-state concentration is below the minimum toxic concentration and calculated trough steady-state concentration is above the minimum effective concentration;

- If necessary, make small adjustments (fine tuning) in the dose and dosing interval.

Drug accumulation (R)

- The administration of a drug in a multiple dose regimen will always result in the accumulation of drug in the body.
- The extent of accumulation (R) of a drug may be quantified in several ways.
- During any dosing interval, the "average" plasma concentration of a drug may be defined as:

$$\left(\bar{C}_p\right)_n = \frac{\int_0^\tau C_{p_n} dt}{\tau}$$

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- Subtituting $\frac{X_O}{V}$ for $\left(C_p\right)_O$ in the equation, $\left(C_{pn}\right)_t = \frac{\left(C_p\right)_O(1-e^{-nK\tau})}{(1-e^{-K\tau})} e^{-Kt}$

- And integrating from t = 0 to t = τ, yields:

$$\int_0^{\tau} C_{p_n} dt = \frac{X_O}{VK}[1 - e^{-nK\tau}]$$

- Dividing both sides by τ:

$$\frac{\int_0^{\tau} C_{p_n} dt}{\tau} = \frac{X_O}{VK\tau}[1 - e^{-nK\tau}]$$

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- Since $\left(\bar{C}_p\right)_n = \frac{\int_0^\tau C_{p_n} dt}{\tau}$,

$$\left(\bar{C}_p\right)_n = \frac{X_O}{VK\tau}\left[1 - e^{-nK\tau}\right]$$

- And, $\left(\bar{C}_p\right)_{ss} = \frac{X_O}{VK\tau}$

- Therefore,

$$\left(\bar{C}_p\right)_n = \left(\bar{C}_p\right)_{ss}\left[1 - e^{-nK\tau}\right]$$

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- Rearranging the above equation:

$$\frac{\left(\bar{C}_p\right)_n}{\left(\bar{C}_p\right)_{ss}} = [1 - e^{-nK\tau}]$$

- When n = 1

$$\frac{\left(\bar{C}_p\right)_1}{\left(\bar{C}_p\right)_{ss}} = [1 - e^{-K\tau}]$$

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- The inverse ratio, $\frac{(\bar{C}_p)_{ss}}{(\bar{C}_p)_1}$, may be defined as an accumulation factor (R);

$$R = \frac{(\bar{C}_p)_{ss}}{(\bar{C}_p)_1} = \frac{1}{[1 - e^{-K\tau}]}$$

- 'R' indicates the extent to which a drug would accumulate in the body.

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- Use of other ratios to calculate drug accumulation:

$$R = \frac{\left(C_{p\infty}\right)_{min}}{\left(C_{p1}\right)_{min}} = \frac{\frac{\left(C_p\right)_O}{\left(1 - e^{-K\tau}\right)} e^{-K\tau}}{\left(C_p\right)_O e^{-K\tau}} = \frac{1}{1 - e^{-K\tau}}$$

- Or

$$R = \frac{\left(C_{p\infty}\right)_{max}}{\left(C_{p1}\right)_{max}} = \frac{\frac{\left(C_p\right)_O}{\left(1 - e^{-K\tau}\right)}}{\left(C_p\right)_O} = \frac{1}{1 - e^{-K\tau}}$$

Determination of fluctuation (Φ):

- Fluctuation is simply a measure of the magnitude of variation (differences) in the peak and trough plasma concentrations at steady state.
    - It is simply a measure of the ratio of the steady-state maximum plasma concentration to the steady-state minimum, or
    - The ratio of the maximum steady-state concentration to the "average" plasma concentration at steady state for the chosen dosage regimen.

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- By comparison of maximum concentration with minimum concentration at steady state:

$$\Phi = \frac{\left(C_{pss}\right)_{max}}{\left(C_{pss}\right)_{min}} = \frac{\dfrac{\left(C_p\right)_O}{(1-e^{-K\tau})}}{\dfrac{\left(C_p\right)_O}{(1-e^{-K\tau})}e^{-K\tau}} = \frac{1}{e^{-K\tau}}$$

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- If the dosing interval (τ) is expressed in terms of number (N) of elimination half lives ($t_{1/2}$), τ = N $t_{1/2}$ and $K = \frac{0.693}{t_{1/2}}$

- Then,

$$\Phi = \frac{1}{e^{-(0.693)(N)}}$$

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Number of doses required to reach steady-state condition

- The plasma concentration at time t after the nth dose is:

$$\left(C_{pn}\right)_t = \frac{\left(C_p\right)_O \left(1 - e^{-nK\tau}\right)}{\left(1 - e^{-K\tau}\right)} e^{Kt}$$

- And the steady-state plasma concentration at time t is:

$$\left(C_{p\infty}\right)_t = \frac{\left(C_p\right)_O}{\left(1 - e^{-K\tau}\right)} e^{-Kt}$$

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$$\frac{\left(C_{pn}\right)_t}{\left(C_{p\infty}\right)_t} = \frac{\frac{\left(C_p\right)_O(1-e^{-nK\tau})}{(1-e^{-K\tau})}e^{Kt}}{\frac{\left(C_p\right)_O}{(1-e^{-K\tau})}e^{-Kt}} = f_{ss} = 1 - e^{-nK\tau}$$

- For τ = N $t_{1/2}$ and $K = \frac{0.693}{t_{1/2}}$

$$f_{ss} = 1 - e^{-0.693nN}$$

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- Taking the natural logarithm and rearrangement of the above equation yields:

$$n = -\frac{\ln(1 - f_{ss})}{0.693N}$$

where n is the number of doses required to reach a given fraction of the steady-state (f_{ss}) condition and N is the number of elimination half lives in the dosing interval.

Loading and Maintenance doses

- It may take a long time and the administration of many doses before the desired "average" steady-state drug concentration is attained.

- Therefore, an IV bolus loading dose (D_L) may be administered to obtain an instant steady-state condition.

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- The calculated D_L should be such that that, at time t after its administration, the plasma concentration of drug is the desired minimum plasma concentration at steady state, that is:

$$\left(C_{pss}\right)_{min} = \frac{D_L}{V} e^{-K\tau}$$

- And we know that,

$$\left(C_{pss}\right)_{min} = \frac{X_O}{V} \frac{e^{-K\tau}}{(1 - e^{-K\tau})}$$

where X_O is the IV bolus maintenance dose (D_M).

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- Then,

$$\frac{D_L}{V}e^{-K\tau} = \frac{D_M}{V}\frac{e^{-K\tau}}{(1-e^{-K\tau})}$$

- Upon simplification and rearrangement, we get:

$$\frac{D_L}{D_M} = \frac{Ve^{-K\tau}}{V(1-e^{-K\tau})e^{-K\tau}} = \frac{1}{1-e^{-K\tau}}$$

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- For τ = N $t_{1/2}$ and $K = \frac{0.693}{t_{1/2}}$

$$\frac{D_L}{D_M} = \frac{1}{1 - e^{-(0.693)(N)}}$$

Multiple-dosage Regimen: EV Administration

- Extravascular delivery is not instantaneous (drug not immediately delivered into the systemic circulation).
- Therefore, the pharmacokinetic equations require a term reflecting an **absorption** process.

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Single extravascular dose

- Over time after an extravascular dose, the amount and concentration of the drug in the body is given by:

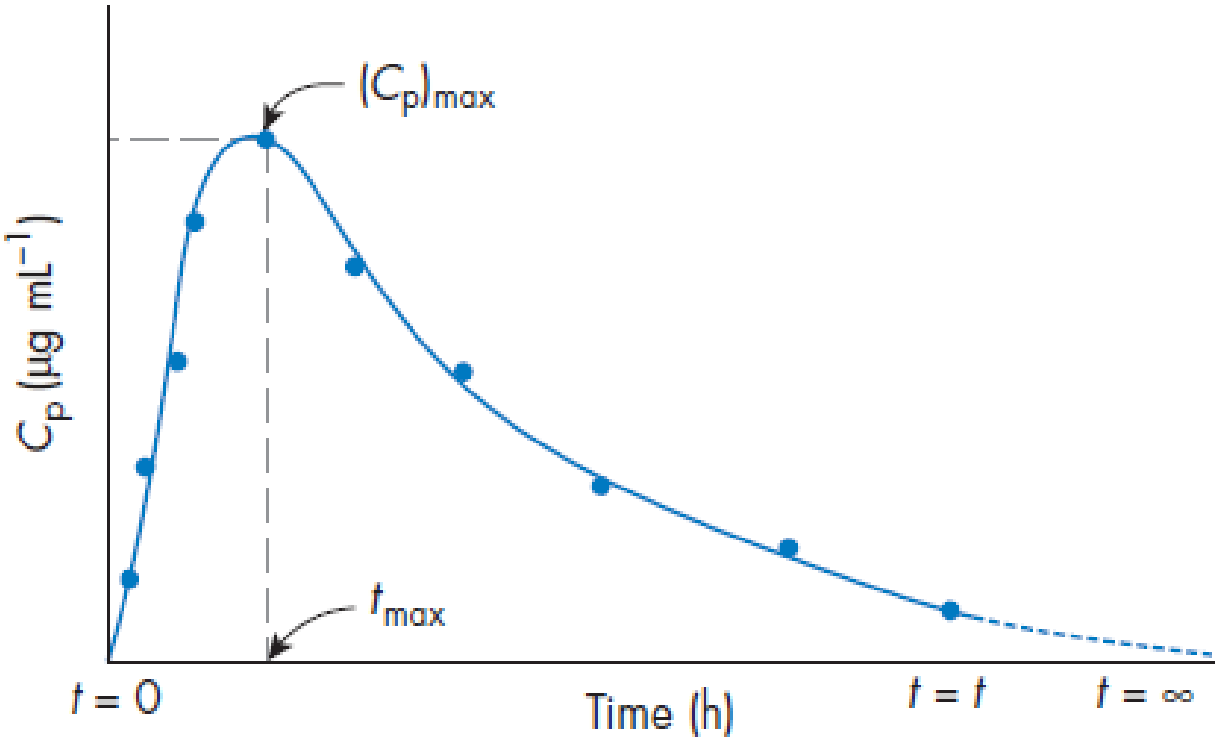
$$(X)_t = \frac{K_a F X_O}{(K_a - K)}(e^{-Kt} - e^{-K_a t})$$

- And,

$$\left(C_p\right)_t = \frac{K_a F X_O}{V(K_a - K)}(e^{-Kt} - e^{-K_a t})$$

...

- From such administration,
  - At $t = 0\ and\ t = \infty$, X = 0 and Cp = 0
  - at $t = t_{max}$ (i.e. peak time), $X = X_{max}$ and $C_p = \left(C_p\right)_{max}$



A typical plasma concentration (Cp) versus time profile for a drug administered as a single dose of drug by an extravascular route.

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Multiple Extravascular Dosing

- The plasma concentration versus time curve following multiple dosing of a drug which is absorbed by an apparent first order process can be described as follows;
  - For a single dose EV administration:

$$\left(C_p\right)_t = \frac{K_a F X_O}{V(K_a - K)}\left(e^{-Kt} - e^{-K_a t}\right)$$

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- And multiplying each exponential term by "r" yields:

$$\left(C_{pn}\right)_t = \frac{K_a F X_O}{V(K_a - K)}\left(\left[\frac{1 - e^{-nK\tau}}{1 - e^{-K\tau}}\right]e^{-Kt} - \left[\frac{1 - e^{-nK_a\tau}}{1 - e^{-K_a\tau}}\right]e^{-K_a t}\right)$$

where $\left(C_{pn}\right)_t$ is the plasma concentration at time t following the administration of the n^{th} dose

- This Eq. may be employed to predict the plasma concentration of drug at any time during the dosing interval following the administration of n^{th} dose.

The peak time in multiple dosing to steady state (t'_{max})

- t'_{max} to steady state ($n = \infty$) can be obtained by differentiating the following equation with respect to time and setting the resultant equal to 0.

$$\left(C_{p\infty}\right)_t = \frac{K_a F X_O}{V(K_a - K)}\left(\left[\frac{1}{1 - e^{-K\tau}}\right]e^{-Kt} - \left[\frac{1}{1 - e^{-K_a\tau}}\right]e^{-K_a t}\right)$$

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- Differentiating the above Eq. with respect to t yields:

$$\frac{d\left(C_{p\infty}\right)_t}{dt} = \frac{K_a F X_O}{V(K_a - K)}\left(\left[\frac{K_a e^{-K_a t}}{1 - e^{-K_a \tau}}\right] - \left[\frac{K e^{-K t}}{1 - e^{-K \tau}}\right]\right)$$

- To find t = t'_{max}, we set the above expression to equal zero, and simplification yields:

$$\frac{K_a e^{-K_a t'_{max}}}{1 - e^{-K_a \tau}} = \frac{K e^{-K t'_{max}}}{1 - e^{-K \tau}}$$

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- Further simplification yields:

$$t'_{max} = \frac{2.303}{K_a - K} \log \left[\frac{K_a}{K} \left(\frac{1 - e^{-K\tau}}{1 - e^{-K_a\tau}} \right) \right]$$

- The peak time following the administration of a single extravascular dose is obtained by:

$$t_{max} = \frac{2.303}{K_a - K} \log \left[\frac{K_a}{K} \right]$$

Maximum plasma concentration at steady state

- Steady state plasma concentration for EV multiple dose administration is obtained by:

$$\left(C_{p\infty}\right)_t = \frac{K_a F X_O}{V(K_a - K)}\left(\left[\frac{1}{1 - e^{-K\tau}}\right]e^{-Kt} - \left[\frac{1}{1 - e^{-K_a\tau}}\right]e^{-K_a t}\right)$$

- And the maximum plasma concentration at steady state is obtained when t = t'_{max}

$$\left(C_{p\infty}\right)_{max} = \frac{K_a F X_O}{V(K_a - K)}\left(\left[\frac{1}{1 - e^{-K\tau}}\right]e^{-Kt'_{max}} - \left[\frac{1}{1 - e^{-K_a\tau}}\right]e^{-K_a t'_{max}}\right)$$

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- From

$$\frac{K_a e^{-K_a t'_{max}}}{1 - e^{-K_a \tau}} = \frac{K e^{-K t'_{max}}}{1 - e^{-K \tau}}$$

- Rearranging for $e^{-K_a t'_{max}}$

$$e^{-K_a t'_{max}} = \left(\frac{1 - e^{-K_a \tau}}{1 - e^{-K \tau}} \right) \frac{K}{K_a} e^{-K t'_{max}}$$

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- Substitution for $e^{-K_a t'_{max}}$ in the Eq. for $\left(C_{p\infty}\right)_{max}$ and rearranging:

$$\left(C_{p\infty}\right)_{max} = \frac{FX_O}{V}\left(\left[\frac{1}{1-e^{-K\tau}}\right]e^{-Kt'_{max}}\right)$$

Minimum plasma concentration at steady state

- Steady state plasma concentration for EV multiple dose administration is obtained by:

$$\left(C_{p\infty}\right)_t = \frac{K_a F X_O}{V(K_a - K)}\left(\left[\frac{1}{1 - e^{-K\tau}}\right]e^{-Kt} - \left[\frac{1}{1 - e^{-K_a\tau}}\right]e^{-K_a t}\right)$$

- And the minimum plasma concentration at steady state is obtained when t = τ

$$\left(C_{p\infty}\right)_{min} = \frac{K_a F X_O}{V(K_a - K)}\left(\left[\frac{1}{1 - e^{-K\tau}}\right]e^{-K\tau} - \left[\frac{1}{1 - e^{-K_a\tau}}\right]e^{-K_a \tau}\right)$$

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- In the post-absorptive phase, the term $e^{-K_a\tau}$ approaches zero.

- Therefore;

$$\left(C_{p\infty}\right)_{min} = \frac{K_a F X_O}{V(K_a - K)}\left(\frac{1}{1 - e^{-K\tau}}\, e^{-K\tau}\right)$$

"Average" plasma concentration at steady state

- The "average" plasma concentration of a drug at steady state for EV administered dose can be calculated from:

$$\left(\bar{C}_p\right)_{ss} = \frac{FX_O}{VK\tau}$$

- The "average" plasma concentration can also be obtained from the area under the plasma concentration time curve during a dosing interval, at steady state.

Drug accumulation

- The accumulation factor (R) following the administration of a drug by an EV route can be calculated by;

$$R = \frac{\left(C_{p\infty}\right)_{min}}{\left(C_{p1}\right)_{min}}$$

- Therefore, substituting for $\left(C_{p\infty}\right)_{min}$ and $\left(C_{p1}\right)_{min}$

$$R = \frac{1}{1 - e^{-K\tau}}$$

- From

$$\left(C_{pn}\right)_t = \frac{K_a F X_O}{V(K_a - K)}\left(\left[\frac{1 - e^{-nK\tau}}{1 - e^{-K\tau}}\right]e^{-Kt} - \left[\frac{1 - e^{-nK_a\tau}}{1 - e^{-K_a\tau}}\right]e^{-K_a t}\right)$$

- We can obtain $\left(C_{p1}\right)_{min}$ at n=1 and t=τ:

$$\left(C_{p1}\right)_{min} = \frac{K_a F X_O}{V(K_a - K)}\left(e^{-K\tau} - e^{-K_a\tau}\right)$$

- And $\left(C_{p\infty}\right)_{min}$ at n = ∞ and t=τ

$$\left(C_{p\infty}\right)_{min} = \frac{K_a F X_O}{V(K_a - K)}\left(\left[\frac{1}{1 - e^{-K\tau}}\right]e^{-K\tau} - \left[\frac{1}{1 - e^{-K_a\tau}}\right]e^{-K_a\tau}\right)$$

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- And, in the post-absorptive phase, the term $e^{-K_a t}$ approaches zero,

- Therefore,

$$\left(C_{p1}\right)_{min} = \frac{K_a F X_O}{V(K_a - K)} e^{-K\tau}$$

- And

$$\left(C_{p\infty}\right)_{min} = \frac{K_a F X_O}{V(K_a - K)} \left(\left[\frac{1}{1 - e^{-K\tau}} \right] e^{-K\tau} \right)$$

Fluctuation factor (Φ)

- To calculate fluctuation at steady state:

$$\Phi = \frac{\left(C_{p_{ss}}\right)_{max}}{\left(C_{p_{ss}}\right)_{min}}$$

- (check for fluctuation with multiple intravenous bolus administration)

Number of doses to reach a fraction of steady state

- The fraction of the steady state following EV administration can be estimated as:

$$f_{ss} = \frac{\bar{C}_{p_n}}{\bar{C}_{p_{ss}}}$$

- Substituting for $\bar{C}_{p_n}$ and $\bar{C}_{p_{ss}}$

$$f_{ss} = 1 + \frac{Ke^{-nK_a t}}{K_a - K} - \frac{K_a e^{-nK\tau}}{K_a - K}$$

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- If $K_a >> K$,

$$f_{ss} = 1 - e^{-nK\tau}$$

- Rearranging and solving for n,

$$n = -\frac{\ln(1 - f_{ss})}{0.693N}$$

Loading and Maintenance Dose

- An initial loading dose may be desirable since a long period of time is required to reach steady state for drugs with long half lives.

- The goal is that $\left(C_{p1}\right)_{min}$ from the loading dose will exactly equal $\left(C_{p\infty}\right)_{min}$ from the multiple-dosing regimen.

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- Hence, equating the two equations:

$$\frac{K_a F(X_O)_{D_L}}{V(K_a - K)}(e^{-K\tau} - e^{-K_a\tau}) = \frac{K_a F(X_O)_{D_M}}{V(K_a - K)}\left[\frac{e^{-K\tau}}{1 - e^{-K\tau}} - \frac{e^{-K_a\tau}}{1 - e^{-K_a\tau}}\right]$$

- Upon rearranging and simplification:

$$(X_O)_{D_L} = (X_O)_{D_M}\left(\frac{1}{(1 - e^{-K_a\tau})(1 - e^{-K\tau})}\right)$$